Genetic studies on the functional relevance of the protein prenyltransferases in skin keratinocytes.

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Authors: Roger Lee, Sandy Y Chang, Hung Trinh, Yiping Tu, Andrew C White, Brandon S J Davies, Martin O Bergo, Loren G Fong, William E Lowry, Stephen G Young

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Public Summary:

Scientific Abstract:
The modification of proteins with farnesyl or geranylgeranyl lipids, a process called protein prenylation, facilitates interactions of proteins with membrane surfaces. Protein prenylation is carried out by a pair of cytosolic enzymes, protein farnesyltransferase (FTase) and protein geranylgeranyltransferase type I (GGTase-I). FTase and GGTase-I have attracted interest as therapeutic targets for both cancer and progeria, but very little information exists on the importance of these enzymes for homeostasis of normal tissues. One study actually suggested that FTase is entirely dispensable. To explore the importance of the protein prenyltransferases for normal tissues, we used conditional knockout alleles for Fntb and Pggt1b (which encode the beta-subunits of FTase and GGTase-I, respectively) and a keratin 14-Cre transgene to create mice lacking FTase or GGTase-I in skin keratinocytes. Keratinocyte-specific Fntb knockout mice were viable but developed severe alopecia. Although hair follicles appeared normal during development, they were morphologically abnormal after birth, and ultrastructural and immunohistochemical studies revealed many apoptotic cells. The interfollicular epidermis of Fntb-deficient mice appeared normal; however, keratinocytes from these mice could not proliferate in culture. As expected, non-farnesylated prelamin A and non-farnesylated DNAJA1 accumulated in Fntb-deficient keratinocytes. Keratinocyte-specific Pggt1b knockout mice survived development but died shortly after birth. Like Fntb-deficient keratinocytes, Pggt1b-deficient keratinocytes did not proliferate in culture. Thus, both FTase and GGTase-I are required for the homeostasis of skin keratinocytes.